Correspondence

Itraconazole-Related Amaurosis and Vomiting Due to Digoxin Toxicity

TO THE EDITOR: The antifungal drug itraconazole is indicated in the treatment of aspergillosis, histoplasmosis, and blastomycosis but has been used to treat other mycoses. The coadministration of other drugs such as histamine H_2 blockers, 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors, warfarin sodium, sulfonylureas, phenytoin, carbamazepine, isoniazid, rifampin, cisapride, tacrolimus, cyclosporine, astemizole, terfenadine, and triazolam can lead to hazardous drug-drug interactions. We have recently encountered a little-appreciated interaction between itraconazole and digoxin.

Report of a Case

Four months after coronary artery bypass grafting, a 67-year-old man noted midback pain. Magnetic resonance imaging of the thoracic spine and computed tomography of the chest revealed diskitis and osteomyelitis at T-7 and T-8, accompanied by a large paravertebral abscess. Fine-needle aspiration of the abscess grew *Candida tropicalis*, which was resistant to fluconazole but sensitive to amphotericin B and itraconazole. Pending sensitivity studies, the patient was treated with the intravenous administration of amphotericin B, 40 mg a day. By the fourth dose, the blood urea nitrogen (BUN) level had risen to 12.5 mmol per liter (35 mg per dl) and the creatinine level to 265 μmol per liter (3.0 mg per dl), and amphotericin B was discontinued, along with digoxin, amiodarone, and glyburide. He was discharged when the BUN level was 4.1 mmol per liter (11.5 mg per dl) and the creatinine level was 130 μmol per liter (1.5 mg per dl) while he was taking his usual medications and itraconazole, 200 mg twice a day.

Ten days later, the patient was readmitted to the hospital because of nausea, vomiting, and a grayish blurring of his vision. His heart rate was 48 beats per minute. The BUN level was 23.5 mmol per liter (66 mg per dl) and the creatinine 220 μmol per liter (2.5 mg per dl) while the serum digoxin level was 8.4 nmol per liter (6.6 ng per ml). Six vials of digoxin immune Fab were administered intravenously. Within 24 hours, the nausea and vomiting resolved, and his vision returned to normal. Azotemia was considered responsible for the digoxin toxicity, and he was discharged on reduced doses of digoxin, amiodarone, glyburide, and itraconazole, 200 mg twice a day. A week later, he was again admitted to the hospital with nausea and blurred vision. His heart rate was 53 beats per minute, and the serum digoxin concentration was 6.1 nmol per liter (4.8 ng per ml). Three vials of digoxin immune Fab were administered intravenously, and within 12 hours the nausea and amaurosis were gone. Itraconazole therapy was discontinued, and the patient received amphotericin B lipid complex without further digoxin toxicity or azotemia. The *C tropicalis* infection was clinically eradicated.

Discussion

Itraconazole-digoxin drug interaction was first described by Rex.[1] Subsequently, three other cases have been reported in detail.[2-4] Sachs and co-workers indicated that itraconazole use substantially increased the half-life of digoxin, necessitating a 60% to 75% reduction in digoxin dosing.[2] A decrease in the rate of digoxin clearance may be responsible for the elevated digoxin levels with itraconazole use. Because itraconazole has no appreciable effect on hepatic microsomal enzymes[5] and the nonrenal clearance of digoxin makes up about 30% of total clearance,[6] it seems unlikely that the inhibition of digoxin biodegradation increased the drug's half-life to the extent noted in these patients.[2]

Of the five reported cases of digoxin toxicity due to itraconazole use, all were in men with a mean age of 72 years. Four of five described visual problems, including xanthopsia, a gray haze, scotomata, and amaurosis, that occurred 7 to 13 days after starting the itraconazole regimen. Because nausea and vomiting can result from the use of itraconazole, the presence of visual symptoms should suggest digoxin toxicity in a patient receiving both drugs.

In our patient, digoxin immune Fab therapy promptly reversed the symptoms of digoxin toxicity.

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